

REMARKS

Upon entry of the above amendment, claims 1-3 and 9-19 will be pending. Claims 1, 9, and 12 are independent claims.

Applicant has amended claim 3 to correct a typographical error. The specification on page 3 provides support for new claims 18 and 19. Applicant has not raised any issue of new matter.

Priority

The Examiner asserts that Applicant has not filed a certified copy of the EP 00201239.1 application as required by 35 U.S.C. §119(b). Applicant has filed the proper documents with WIPO. Applicant has attached a copy of Form PCT/IB/304 that indicates that Applicant has filed the priority document on July 9, 2001.

Applicant respectfully requests the Examiner to WIPO to send a copy of the priority document.

Issue Under 35 U.S.C. §103(a)

Claims 1-3 and 9-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lange et al (Drugs under Experimental and Clinical Research, 1995, 21(3), 89-96) in view of Olsen '674

(WO 9819674). Applicant asserts that patentable distinctions exist between the cited prior art and the present invention.

Distinctions Between the Present Invention and Lange et al in view of Olsen '674

Lange et al discloses the safety and efficacy of treatment of tension-type headache with either ketoprofen or ibuprofen. Lange et al. fails to disclose a pharmaceutical combination of a NSAID with any other pharmaceutical compound.

Olsen '674 discloses on page 32, lines 7-13 that mirtazapine "may also have an effect on glutamine neurotransmission, potentially as non-competitive NMDA receptor antagonists. It is through this mechanism that [mirtazapine is] presumed to provide a method of treatment of tension-type headaches." The only demonstrated anti-headache effects in Olsen '674 are with L-NMMA (page 74-75), Gabapentin (page 91) and Dextromethorphan (page 93). Olsen '674 provides no mechanistic or structural relation between the exemplified drugs and mirtazapine.

Olsen '674 fails to provide any data to support its assertion; therefore, Olsen '674 is merely speculating as to the action of mirtazapine and many other compounds. For example as to the speculation within Olsen '674, Applicant directs the Examiner to speculative claim 14 where Olsen '674 appears recite every possible mechanistic relationship without any support. More importantly, Olsen '674 fails to disclose any combination

composition for treatment of headaches containing mirtazapine and a NSAID.

The Examiner asserts that a skilled artisan would combine the two cited references to render the present invention obvious because both compounds are "known" treatments of tension-type headaches. As indicated above, Olsen '674 only speculates that mirtazapine might provide a treatment, but provides no actual support for its assertion. Neither reference discloses or suggests combination treatments with mirtazapine. In addition, neither reference suggest the dosage range of 0.1 to 5mg as claimed in claims 10, 13, 15 and 17.

The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of making the present invention. "To prevent the use of hindsight **based on the invention** to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and **with no knowledge of the claimed invention**, would select the elements from the cited prior art references for combination in the manner claimed. In re Rouffet, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998).

Clearly, cited prior art fails to motivate a skilled artisan to make the present pharmaceutical combination of mirtazapine and a NSAID.

Applicant respectfully requests withdrawal of the 35 U.S.C. §103(a) rejection.

Concurrently Filed Information Disclosure Statement

Applicant has filed an IDS concurrently with this amendment and remarks. Applicant believes that these references are not relevant as to the patentability of the present application. Two of the references are self-explanatory. The Demling reference is in German and discusses mianserin and its efficacy against tension headaches. See page 72, left column "war Mianserin gegen Spannungskopfschmerzen." Mirtazapine is discussed as a related compound, but it is stated that there is considerable distinction in pharmacological properties. See page 72, middle column "ein erheblicher Unterschied zwischen beiden Verbindungen in der Verteilung der Elektronendichte und damit auch in den pharmakologischen Eigenschaften." Applicants can prepare an English translation, if the Examiner deems it necessary.

Conclusion

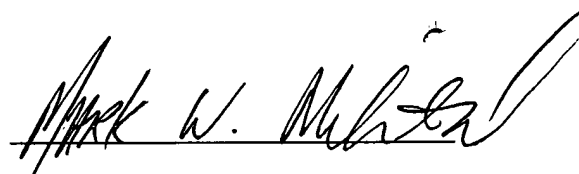
All the stated grounds of the rejections have been properly traversed, accommodated or rendered moot. Applicant respectfully submits that the present application is in condition for

allowance.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Mark W. Milstead", is written over a horizontal line.

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Enclosure: Form PCT/IB/304